General

Guideline Title

Evidence-based care guideline for cytomegalovirus prevention following solid organ transplantation.

Bibliographic Source(s)

Cincinnati Children's Hospital Medical Center. Evidence-based clinical care guideline for cytomegalovirus prevention following solid organ transplantation. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2013 Sep 30. 10 p. [50 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Cincinnati Children's Hospital Medical Center. Evidence-based care guideline for cytomegalovirus prophylaxis following solid organ transplants. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2007 Jul 6. 15 p. [68 references]

Recommendations

Major Recommendations

The strength of the recommendation (strongly recommended, recommended, or no recommendation) and the quality of the evidence (1aâ€'5b) are defined at the end of the "Major Recommendations" field.

Assessment

Laboratory Assessment/Monitoring

1. It is recommended:
   - That whole blood cytomegalovirus (CMV) deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) be used for monitoring (Lisboa et al., 2011 [4b (diagnosis)]), and
   - That monitoring occur at specified intervals (see Table 2 in original guideline document) (Local Consensus, 2013 [5]).
2. It is recommended, to assure consistent results, that the same laboratory facility and assay be used for serial samples (Local Consensus, 2013 [5]; Pang et al., 2009 [5a (diagnostics)])
   Note 1: The laboratory facility at Cincinnati Children's Hospital Medical Center (CCHMC) will be used for CCHMC patients.

   Note 2: Inconsistent test results may be the result of testing being performed:

   - At different laboratory facilities
   - Using different assays
   - On a different specimen type (e.g., whole blood vs. plasma) (Lisboa et al., 2011 [4b (diagnosis)])

Contributing factors may be:

- Patient use of different laboratory facility due to geographic need or insurance
- The designated laboratory facility transitions to use a different assay
- Unreliable implementation processes (see the "Description of Implementation Strategy" field and Appendix 2 in the original guideline document)

Clinical Assessment

3. It is recommended that patients with any of the following clinical conditions be evaluated for CMV by examination, whole blood PCR and end-organ histopathology if indicated (Local Consensus, 2013 [5]; Kotton et al., 2013 [5a]):
    - Fever
    - Hepatitis
    - Muscle pain
    - Gastroenteropathy
    - Leukopenia
    - Pneumonitis
    - Thrombocytopenia
    - Retinitis
    - Anemia

Management Recommendations

General

Recommendations for CMV disease prevention in solid organ transplant recipients are based on the organ transplanted and previously defined risk levels (see Table 2 in original guideline document).

Primary Strategy

4. It is recommended that targeted prophylaxis be the primary strategy for prevention of CMV disease at CCHMC (Local Consensus, 2013 [5]). See the definition for "targeted prophylaxis" on Page 1 of the original guideline document.

Risk Stratification

5. It is recommended that targeted prophylaxis be risk stratified based on donor/recipient (D/R) CMV serostatus (see Table 2 in the original guideline document) (Local Consensus, 2013 [5], Kotton et al., 2013 [5a]).
6. It is recommended to assign infants <12 months of age to the high risk category unless D-/R-, as serology in infants <12 months of age may be confounded by maternal antibody (see Table 3 in the original guideline document) (Local Consensus, 2013 [5]; Kotton et al., 2013 [5a]).

Medications

7. It is recommended to use age- and weight-based antiviral dosing (see Table 4 in the original guideline document) (Villeneuve et al., 2013 [3a (treatment)]; Launay et al., 2012 [3a (treatment)]; Pescovitz et al., 2010 [3a (treatment)]; Vaudry et al., 2009 [3a (treatment)]; Local Consensus, 2013 [5]).
8. It is recommended that valganciclovir (VGCV) be dosed around a meal (Villeneuve et al., 2013 [3a (treatment)]; Pescovitz et al., 2010 [3a (treatment)]).

Definitions:

Table of Evidence Levels

Quality Level	**Definition**
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain

Quality Level	Definition
4a or 4b	Weak study design for domain
5, 5a or 5b	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

Table of Recommendation Strength

Strength	Definition
"Strongly Recommended"	There is consensus that benefits clearly outweigh risks and burdens (or vice versa for negative recommendations).
"Recommended"	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.

Note: See the original guideline document for the dimensions used for judging the strength of the recommendation.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Cytomegalovirus (CMV) infection and disease following solid organ transplants

Guideline Category

Evaluation

Management

Prevention

Risk Assessment

Clinical Specialty

Cardiology

Critical Care

Gastroenterology

Hematology

Infectious Diseases

Internal Medicine

Nephrology

Pathology

Pediatrics

Preventive Medicine

Pulmonary Medicine

Surgery

Intended Users

Advanced Practice Nurses

Nurses

Patients

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To prevent cytomegalovirus (CMV) disease in at-risk solid organ transplant recipients through risk stratification and targeted and cost-effective prevention strategies

Target Population

Patients with solid organ transplant, ages birth to young adults

Note: These recommendations are NOT intended for use in the following:

Patients with cytomegalovirus (CMV) disease
Patients with non-solid organ transplants

Interventions and Practices Considered

Evaluation/Risk Assessment

1. Use of whole blood cytomegalovirus (CMV) deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) for monitoring at specified intervals
2. Using the same laboratory facility and assay for serial samples
3. Clinical assessment of patients if certain conditions indicate

Prevention/Management

1. Targeted prophylaxis with risk stratification based on donor/recipient CMV serostatus
2. Age- and weight-based antiviral dosing
3. Prophylactic antiviral therapy:
    - Ganciclovir
    - Valganciclovir (VGCV)

Major Outcomes Considered

- Risk for cytomegalovirus (CMV) infection
- Consistency of laboratory assays for CMV

- Epidemiology of CMV by organ type
- Incidence of CMV infection following prophylactic therapy
- Adverse effects of prophylactic therapy

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

To select evidence for critical appraisal by the group for this guideline, the MEDLINE, EMBASE and the Cochrane databases were searched for dates of January 2007 to August 2013 to generate an unrefined, "combined evidence" database using a search strategy focused on answering clinical questions relevant to cytomegalovirus and solid organ transplantation and employing a combination of Boolean searching on human-indexed thesaurus terms (MeSH headings using an OVID MEDLINE interface) and "natural language" searching on words in the title, abstract, and indexing terms. The citations were reduced by: eliminating duplicates, review articles, and non-English articles. The resulting abstracts were reviewed to eliminate low quality and irrelevant citations. During the course of the guideline development, additional clinical questions were generated and subjected to the search process. January 2007 was the last date for which literature was reviewed for the previous version of this guideline. All previous citations were reviewed for appropriateness to this revision.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Table of Evidence Levels

Quality Level	Definition
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5, 5a or 5b	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The process by which this guideline was developed is documented in the Guideline Development Process Manual (see the "Availability of Companion Documents" field); relevant development materials are kept electronically. The recommendations contained in this guideline were formulated by an interdisciplinary working group which performed systematic search and critical appraisal of the literature, using the Table of Evidence Levels (see the "Rating Scheme for the Strength of the Evidence field"), and examined current local clinical practices.

Recommendations have been formulated by a consensus process directed by best evidence, patient and family preference and clinical expertise. During formulation of these recommendations, the team members have remained cognizant of controversies and disagreements over the management of these patients. The team tried to resolve controversial issues by consensus where possible and, when not possible, to offer optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices.

Rating Scheme for the Strength of the Recommendations

Table of Recommendation Strength

Strength	Definition
"Strongly Recommended"	There is consensus that benefits clearly outweigh risks and burdens (or vice versa for negative recommendations).
"Recommended"	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.

Note: See the original guideline document for the dimensions used for judging the strength of the recommendation.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

The recommendations have been reviewed and approved by clinical experts not involved in the development process and distributed to other parties as appropriate to their intended purposes.

Evidence Supporting the Recommendations

References Supporting the Recommendations

References Supporting the Recommendations

Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S, Danziger-Isakov L, Humar A, Transplantation Society International CMV Consensus Group. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation. 2013 Aug 27;96(4):333-60. PubMed

Launay E, Theoret Y, Litalien C, Duval M, Alvarez F, Lapeyraque AL, Phan V, Larocque D, Poirier N, Lamarre V, Ovetchkine P. Pharmacokinetic profile of valganciclovir in pediatric transplant recipients. Pediatr Infect Dis J. 2012 Apr;31(4):405-7. PubMed

Lisboa LF, Asberg A, Kumar D, Pang X, Hartmann A, Preiksaitis JK, Pescovitz MD, Rollag H, Jardine AG, Humar A. The clinical utility of whole blood versus plasma cytomegalovirus viral load assays for monitoring therapeutic response. Transplantation. 2011 Jan 27;91(2):231-6. PubMed

Pang XL, Fox JD, Fenton JM, Miller GG, Caliendo AM, Preiksaitis JK, American Society of Transplantation Infectious Diseases Community of Practice, Canadian Society of Transplantation. Interlaboratory comparison of cytomegalovirus viral load assays. Am J Transplant. 2009 Feb;9(2):258-68. PubMed

Pescovitz MD, Ettenger RB, Strife CF, Sherbotie JR, Thomas SE, McDiarmid S, Bartosh S, Ives J, Bouw MR, Bucuvalas J. Pharmacokinetics of oral valganciclovir solution and intravenous ganciclovir in pediatric renal and liver transplant recipients. Transpl Infect Dis. 2010 Jun;12(3):195-203. PubMed

Vaudry W, Ettenger R, Jara P, Varela-Fascinetto G, Bouw MR, Ives J, Walker R, Valcyte WV16726 Study Group. Valganciclovir dosing according to body surface area and renal function in pediatric solid organ transplant recipients. Am J Transplant. 2009 Mar;9(3):636-43. PubMed

Villeneuve D, Brothers A, Harvey E, Kemna M, Law Y, Nemeth T, Gantt S. Valganciclovir dosing using area under the curve calculations in pediatric solid organ transplant recipients. Pediatr Transplant. 2013 Feb;17(1):80-5. PubMed

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Prevention or decreased incidence of cytomegalovirus (CMV) infection and cytomegalovirus disease and its associated significant morbidity and mortality after solid organ transplantation

Potential Harms

- Valganciclovir (VGCV) and ganciclovir toxicity includes neutropenia, thrombocytopenia, and renal dysfunction require regular monitoring.
- Use caution with VGCV in patients with small bowel transplants due to concerns for malabsorption.

Qualifying Statements

Qualifying Statements

These recommendations result from review of literature and practices current at the time of their formulations. This guideline does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the guidelines to meet the specific and unique requirements of individual patients. Adherence to this guideline is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

Implementation of the Guideline

Description of Implementation Strategy

Implementation Issues for Cytomegalovirus (CMV) Monitoring Related to External Laboratory Facility Use

Attempts to implement Recommendation #2 may encounter difficulties when use of external laboratory facilities cannot be avoided. Under such circumstances, a reliable process to document the following relevant details will enable appropriate interpretation of assay results.

Specifics to be documented for each specimen:

1. Laboratory facility
2. Specimen type (whole blood or plasma)
3. Unit of measure for results (copies/mL, IU/mL, etc.)
4. Assay used (if available)

In addition, implementation of this interpretation requires reliable access to these details within the context of clinic flow.

Implementation Tools

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2001 Jun 7 (revised 2013 Sep 30)

Guideline Developer(s)

Cincinnati Children's Hospital Medical Center - Hospital/Medical Center

Source(s) of Funding

Cincinnati Children's Hospital Medical Center

The guideline was developed without external funding.

Guideline Committee

Cytomegalovirus (CMV) Prevention following Solid Organ Transplantation Team 2013

Composition of Group That Authored the Guideline

Cincinnati Children's Hospital Medical Center Physicians: Lara Danziger-Isakov, MD, MPH, Infectious Diseases (*Chair*); John Bucuvalas, MD, Liver Transplant; Rohit Kohli, MD, Liver Transplant; Chesney Castleberry, MD, Cardiology/Transplant; Samuel Kocoshis, MD Intestinal Transplant; Jens Goebel, MD, Nephrology/Transplant; Marc Schechter, MD, Pulmonary/Transplant; David Witte, MD, Pathology

Patient Services: Trina Hemmelgarn, Pharmacy, PharmD; Danielle Lazear, Pharmacy, PharmD

Other Team Members: Michael Lake, Transplant Analytics, MA

Professional Support Staff: Eloise Clark, MPH, MBA, Methodologist, James M. Anderson Center for Health Systems Excellence; Scott Wansley, Transplant Administration, MBA

Financial Disclosures/Conflicts of Interest

All Team Members and Clinical Effectiveness support staff listed have declared whether they have any conflict of interest and none were identified. Conflict of interest declaration forms are on file with the Evidence group of the James M. Anderson Center for Health Systems Excellence.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cincinnati Children's Hospital Medical Center Web site .

Print copies: For information regarding the full-text guideline, print copies, or evidence-based practice support services contact the Cincinnati Children's Hospital Medical Center Health James M. Anderson Center for Health Systems Excellence at EBDMInfo@cchmc.org.

Availability of Companion Documents

The following are available:

- Evidence-based care guideline development and update process. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2006 Mar. 35 p. Available from the Cincinnati Children's Hospital Medical Center (CCHMC) Web site .
- Judging the strength of a recommendation. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2009 May 7. 1 p. Available from the CCHMC Web site .
- Grading a body of evidence to answer a clinical question. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2009 May 7. 1 p. Available from the CCHMC Web site .
- Table of evidence levels. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2009 May 7. 1 p. Available from the CCHMC Web site .

Print copies: For information regarding the full-text guideline, print copies, or evidence-based practice support services contact the Cincinnati Children's Hospital Medical Center Health James M. Anderson Center for Health Systems Excellence at EBDMInfo@cchmc.org.

Patient Resources

The following are available:

- Medications to prevent infection following kidney transplant. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2012 Dec. Electronic copies: Available from the Cincinnati Children's Hospital Medical Center (CCHMC) Web site .
- Cytomegalovirus (CMV) in the immunocompromised patient. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2013 Jul. Electronic copies: Available from the CCHMC Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI on March 11, 2004. This NGC summary was updated by ECRI Institute on February 26, 2008. This summary was updated by ECRI Institute on October 5, 2010 following the U.S. Food and Drug Administration (FDA) advisory on valcyte (valganciclovir hydrochloride). This summary was updated by ECRI Institute on January 20, 2014.

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